TIP30, a cofactor for HIV-1 Tat-activated transcription, is homologous to short-chain dehydrogenases/reductases

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Human TIP30 is a cofactor that specifically enhances human immunodeficiency virus-1 (HIV-1) Tat-activated transcription [1]. The sequence of human TIP30 is 98% identical to human CC3, a protein associated with the suppression of metastasis in small cell lung carcinomas [2]. CC3 is also expressed in a variety of cells, including heart, brain, lung, kidney, skeletal muscle and pancreas, in which its function is unknown. A pairwise gapped BLAST comparison [3] of *Aquifex aeolicus* 2982870, which belongs to the short-chain dehydrogenase/reductase (SDR) family [4], with TIP30 yielded an E-value of 3×10^{-4}, indicating that TIP30 also belongs to the SDR family. Because of the unusual nature of this discovery, we also investigated the ancestry of human TIP30 with the PSI-BLAST database-searching program, using as cutoff an E-value of 10^{-5} for including a protein in the position-dependent scoring matrix. (The default cutoff was an E-value of 10^{-3}.) Thus, *A. aeolicus* 2982870 was not included in the first iteration. Nevertheless, the first PSI-BLAST iteration yielded an E-value of 10^{-10} for *A. aeolicus* 2982870. Moreover, the third PSI-BLAST iteration yielded an E-value of 7×10^{-21} for *Escherichia coli* UDP-galactose-4-epimerase, a known SDR [5,6].

Figure 1 shows a sequence alignment of TIP30, *A. aeolicus* 2982870 and *E. coli* UDP-galactose-4-epimerase. The amino terminus of TIP30 has the Gly-Xaa-Xaa-Gly-Xaa-Xaa-Gly motif (in which Xaa represents any amino acid) found in the nucleotide cofactor binding domain. Furthermore, Ser132, Tyr143 and Lys147 align with the known active residues in the catalytic site of SDRs [4–10]. Residues in the carboxy-terminal third of TIP30 and CC3 correspond to the SDR substrate-binding site.

Although most SDRs are oxidoreductases, spinach CSP41, which binds mRNA and has ribonuclease activity, was recently shown to belong to the SDR family [11]. Whatever TIP30's enzyme activity is, it may be important in enhancing transcription of HIV-1 Tat, in which case, inhibitors of TIP30 would be useful for controlling replication of HIV-1. Similarly, elucidation of the enzymatic activity of CC3 could lead to strategies for controlling metastasis of small cell lung carcinomas, as well as elucidating CC3's function in normal cells.

Figure 1

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Human TIP30                  21 VFILGASGETGRVLLKEILEQGLFSKVTLIGRRKLT----FDEEAYKN-VNQEVVDFEKLDD
A. aeolicus 2982870           3 VFITGATGFVGRHIVRELLNRGY---EVHAGVRNLS----KLERLFGNQVKGYIVNFDEKDS
UDP-galactose 4-epimerase     3 VLVTGGSGYIGSHTCVQLLQNGHDVIILDNLCNSKRSVLPVIERLGGKHPTFVEGDIRNEAL

Human TIP30                  78 YASA-------FQGHDVGFCCLGTTRGKAGAEGF--VRVDRD---YVLKSAELAKAGGCKHF
A. aeolicus 2982870          58 IREALGKVNPDFVIHLIGILYEEKKKGIT----F--ERVHYG---HTKNLVEVSKGFNVKKF
UDP-galactose 4-epimerase    65 MTEI-------LHDHAIDTVIHFAGLKAVGESVQKPLEYYDNNVNGTLRLISAMRAANVKNF

                                    *                       *   *
Human TIP30                 128 NLLSSKGADKSSN--------------FLYLQVKGEVEAKVE--ELKFDRYSVFRPGVLLC 172
A. aeolicus 2982870         111 LFMSALGTHDEAP--------------SRYHQTKRWAEREVI--NSGLN-YTIFRPSIILG 154
UDP-galactose 4-epimerase   120 IFSSSATVYGDQPKIPYVESFPTGTPQSPYGKSKLMVEQILTDLQKAQPDWSIALLRYFNP 180
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Sequence alignment of human TIP30 with *A. aeolicus* 2982870 and *E. coli* UDP-galactose 4-epimerase. Glycine residues in the nucleotide-binding domain are shown in bold; the catalytically important serine (S), tyrosine (Y) and lysine (K) residues are underlined and marked with an asterisk.

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